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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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WOLF GREENFIELD & SACKS, PC
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/754,911	TING, ALICE Y.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2005 and 09 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57,81,95,110,111,122 and 146* is/are pending in the application.

4a) Of the above claim(s) *3,5-29,34,36,41-51,57,81,95,111,122 and 146* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,30-33,35,37-40 and 52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-57, 81, 95, 110-111, 122 and 146 are pending

Claims 3, 5-29, 34, 36, 41-51, 57, 81, 95, 111, 122 and 146 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species.

Claims 58-80, 82-94, 96-109, 112-121, 123-145 and 147-161 have been cancelled.

Claims 1, 2, 4, 30-33, 35, 37-40 and 52-56 are under examination.

Information Disclosure Statement

Applicants state that the returned 1449 form does not indicate whether the Saxon et al reference has been considered.

In response, the inadvertent omission of the line drawn through this reference is regretted. (Note however, that the reference contain a dot indicating it has been considered). A signed copy of 1449 is attached herein.

The IDS of 2/9/2006 in reference to the copending application, S.N. 11/262325, filed on October 28, 2005 has been considered.

Drawings

The objection to the drawings due to the lack of Seq. ID. NO. has been obviated with applicants' statement that Fig. 7 provides Seq. ID. Nos. 1 and 2, respectively.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, first paragraph

Claims 1, 2, 4, 30-33, 35, 37-40 and 52-56, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and reiterated below.

To satisfy a written description requirement for a claimed genus a sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such

identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

The specification at paragraph [0179](U.S. 2004/0209317) describes as an example, mutant BirA that can be applied to the study of PI3-kinase activation in 3T3-L1 adipocytes. These adipocytes display a membrane ruffling response to PDGF and a glucose transport response to insulin, both mediated by PI3-kinase stimulation. These differing downstream effects may result, according to one hypothesis, from activation of spatially and/or temporally separate pools of PI3-kinase. To test this, a two-tag FRET system is constructed by enzymatically labeling the catalytic and regulatory subunits of PI3-kinase inside cells. Small fluorophores should perturb the system far less than fluorescent proteins such as GFP. This system allows measurement of PI3-kinase activation in real time and at subcellular resolution after insulin or PDGF stimulation. This description relates to studies that should be performed for the claimed method. It is not apparent whether said method has actually been reduced to practice. This generic description is as generic as claimed. The claims do not recite for any structure of the component methods such as fusion protein, biotin analog, and biotin ligase mutant. Each of these

components e.g., biotin analog covers a huge scope. The generalities made in the specification would not be a sufficient written description for said genus claims. As applicant states at paragraph [0162]ketone biotin analog (FIG. 1B) is not by itself a biophysical probe, but once conjugated to a protein of interest, can serve as a chemical handle for selective derivatization with hydrazine or alkoxyamine-bearing probes (FIG. 2). This chemistry is specific for the introduced ketone over other functionalities present on mammalian cell surfaces. (Mahal et al. Science 276:1125-1128, 1997.) Inside a cell, hydrazides must be prevented from coupling to ketone and aldehyde carbonyls of carbohydrates and natural cofactors. At . Paragraph [0176] the disclosure states that the third mutant BirA expression level must be high enough that target proteins will be labeled efficiently. However, overexpression can lead to toxicity. The selection strategy in some instances would favor a stable cell line that expresses the mutant BirA consistently and at moderate levels. Schatz (Biotechnology) at page 1138, col. 2 states that very few protein are biotinylated, only one in E. coli, three in Saccharomyces Cerivisea and four in mammalian cell. This tightly restricted specificity of biotinylation results from the recognition by biotin holoenzyme synthetase of a complex protein domain. These biotinylated domains are highly

conserved in a wide variety of species and reside in 80 amino acid regions surrounding the modified lysine. Changes in this domain as far as 33 or more residues from the modified K can abolish biotinylation, presumably because the synthetase recognizes a folded structure. In biotechnological invention one cannot necessarily claim a genus after only describing a limited number of species. There may be unpredictability in the results obtained from species other than those specifically described. This is evident from the disclosure as stated above and Schatz reference. When there is substantial variation within the genus (e.g., mutant and analogs), one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

Applicants, at the time of filing, are deemed to have not invented species sufficient to constitute the genus by virtue of having disclosed a single species when the evidence indicates ordinary artisans could not predict the operability in the

invention of any species other than the one disclosed. In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

Response to Arguments

Applicant states that the specification describes and provides examples of target proteins (see paragraphs (0012) and (0065)), acceptor peptides (see paragraphs (0013) and (00691), and methods of conjugating the two (see paragraphs (0013), (0070) and (00711). The specification provides genus definitions as well as numerous species of biotin analogs and biotin ligase mutants. A biotin ligase mutant is defined as a variant of biotin ligase that is enzymatically active towards a biotin analog. (See paragraph (00731.) Biotin ligase is BirA, the 321 amino acid sequence of which is provided as SEQ ID NO:1. The specification teaches that the biotin ligase mutant can have various mutations, including addition, deletion or substitution or one or more amino acids and that preferably, the mutation will be present in the biotin interaction and activation region, spanning amino acids 83-235 but not at positions 1-26 or 1-83. (See paragraph (00741.) Thus, the genus of "biotin ligase mutants" comprises species with substantial sequence similarity. The specification further identifies residue positions 83, 89- 91, 107, 1 12, 1 15-1 18, 123, 142,

186, 1 89, 190, 204, 206, 207 and 235 (relative to the wild type biotin ligase amino acid sequence) as being particularly important for biotin interaction and affinity. A number of species of biotin ligase mutants is also provided including T90G, T90A, T90V, C107G, Q112M, G115A, Y132A, Y132G, S134G, V189G, 1207S, T90Gm91S, T90G/N91G, T90A/N91A, T90A/N91A, T90Am91L and T90Vm91L. Accordingly, based on the common characteristics within the genus, a representative number of species has been identified.

In reply, it is not controverted that the specification discloses species of e.g., the mutations at some specific locations of the sequence with specific residues. Neither does the definition of the terms are controverted, which as applicant recognized is well known in the art. Rather, the issue is if specific mutations with the specific residues at the specific position of the peptide sequence are correlatable to the huge scope of the claimed mutations. The claimed mutation, inter alia, covers mutating any of the residues, singly or in combination, other than those specifically recited therein. For example, it is not apparent whether the other recited positions would have the same residue substitution(s) as the other specifically recited ones.

Applicant states that Schatz is directed at identifying consensus sequences of peptides that can be biotinylated by BirA biotin ligase. Accordingly, the reference supports rather than refutes the existence of peptides that can be attached to target proteins and subsequently biotinylated. Thus, as evidenced by the art cited by the Examiner (in particular the Schatz literature reference and patents), acceptor peptides, their conjugation to target proteins, and their subsequent biotinylation were known in the art at the time of filing.

In reply, Schatz discloses the known biotinylation process as stated. However, Schatz discloses specific biotinylation of a consensus sequences with specific residues. However, unlike the instant claims, Schatz does not correlate the specific components to a genus component(s). As applicant states below, Schatz does not disclose mutating BIR at specific locations with specific residues, let alone, as the claimed genus.

Applicants argue that the specification provides a representative number of species for each claim limitation and such number is sufficient to support each claimed genus. Applicant states that the instant specification identifies the claimed genera, and it provides multiple examples of species within the genera. It therefore sufficiently describes the genus commensurate with the scope of the claims.

In reply, it is not seen how the eight species of a 321-residue protein can sufficiently describe the genus of said 321-residue protein ligase. It is the nature of the invention. A skilled artisan would not be able to apprised from the specific amino acid substitutes the one that can be apply to the other positions of any type of amino acids in the 321 long ligase. This is especially true since applicant asserts that she is the first to discover such mutation in the ligase that results in better(?) labeling of biotin. The other disclosed positions simply list said positions without reciting, importantly, the residue substitutes for each of these positions, singly or in combination. At the time of filing applicant is not in possession of the claimed genus or the species for each of the disclosed other positions.

Applicant states that In Eli Lilly, claims to human insulin encoding genes were found not to be supported by a specification that disclosed only a single mouse insulin gene and provided no structural information for the claimed genus. The specification did not disclose any common distinguishing features possessed by the members of the genus. In Noelle, claims to a genus of antibodies to CD40CR were found not to be supported by a specification that described only mouse CD40CR and did not disclose any features shared by CD40CR from different species.

The instant specification, in contrast, describes features common to the genus, as described herein.

In reply, the instant genus of structurally undefined fusion protein with a biotin analog, acceptor peptide does not share a common feature. The ligase recites a wild-type structure which is not a common feature since it has to be mutated in order to effect labeling.

Claims 1, 2, 4, 30-33, 35, 37-40 and 52-56, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, as reiterated below.

The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(1) the breadth of the claims,
(2) the nature of the invention,
(3) the state of the prior art,
(4) the level of one of ordinary skill;
(5) the level of predictability in the art,
(6) the amount of direction provided by the inventor,
(7) the existence of working examples, and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, (U.S.P.Q. 2d 1400 (CAFC 1988).

1). The specification fails to give adequate direction and guidance in how to readily go about determining which target protein can be labeled by a fusion protein with biotin analog, and biotin ligase mutant.

2). The specification failed to provide working examples for the numerous and different type of biotin analog, target protein, biotin ligase mutant and acceptor peptide. The claimed biotin analog or ligase mutant covers a broad scope of mutations e.g., substitution, addition, deletion in the parent ligase, either singly or in combination.

3). The breadth of the claims encompasses a large diversity of biotin analog, ligase, and acceptor peptide and target protein to enable specific labeling of a target protein. See the statement in the disclosure, as stated above.

4). The state of the prior art is such that techniques or methods are specifically applied or adapted for a known or defined structure of a specific acceptor peptide and biotin present in a specific prokaryote or eukaryote.

5). The art is inherently unpredictable because it is not possible to predict which analogs or mutant would reliably predict labeling a specific target protein. See Schatz and applicant's disclosure above.

6). Because the art is unpredictable, applicants' specification reasonably would not have assured persons skilled in the art to the numerous undefined variables of the claimed method e.g., microorganism(s) and/or eukaryote(s) containing biotin, acceptor peptide, target protein, analog of biotin and mutant ligase. Applicants do not adequately enable persons skilled in the art to readily determine such. Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success.

Response to Arguments

Nature of the Invention: The claimed invention is premised on the finding that the strict fidelity of wild type biotin ligase for biotin can be eased to create variants of biotin ligase that have a relaxed substrate specificity that includes specificity for biotin analogs, optionally to the exclusion of biotin.

In reply, the specification does not describe that the broad genus of a mutated ligase and the other undefined components result in a specificity reaction for all the components used in the method.

Breadth of the Claims: Each of claimed terms is structurally and functionally defined in the specification and examples of each are provided in the specification. The sequences of various biotin ligase mutants are provided as are the chemical structures of various biotin analogs. The sequences of various acceptor peptides are also provided. The target protein can be any protein which can be conjugated to the acceptor peptide either at the nucleic acid or amino acid level.

In response, the specification does not provide reasonable assurance that the examples in the specification could be extrapolated to the broad claimed genus.

State of the Art: The state of the art is exemplified by the Schatz reference and patents cited to and from the Examiner. The art was familiar with the ability to exploit the specificity of wild type biotin ligase in order to biotinylate a target protein for the purpose of labeling and monitoring such protein. The art had identified consensus sequences for acceptor peptides that are biotinylated by biotin ligase, and fusion of the acceptor peptide to a target of interest was routine. The Schatz patents of record clearly demonstrate a number of acceptor peptides that can be fused to any target protein, thereby

allowing such protein to be biotinylated by biotin ligase. The Schatz patents demonstrate the specificity that biotin ligase has for such acceptor peptides and thus the specificity of biotinylation of any fusion proteins that comprise the acceptor peptide provided biotin ligase is present.

In response, the Schatz reference, as applicant stated above deals with identifying consensus sequence of the acceptor peptide and not mutation of the BIR. The art at the time of filing, as applicant states, is still under exploratory study in mutating the wild-type ligase. It is apparent from the prior art that labeling of specific biotin analog is by the wild-type ligase. It is however still uncertain whether a specific mutation, let alone, a multitude of mutations would result in the labeling of an unknown target protein. Applicant is claiming that she is the first to discover such.

Level of Ordinary Skill in the Art: The level of ordinary skill in the art is also exemplified by the Schatz patents of record. The ordinary artisan would be familiar with, inter alia, isolation and mutation of biotin ligase genes and proteins, synthesis of fusion proteins at either the nucleic acid or amino acid level, and biotinylation assays.

In response, except for the Schatz patents, applicant has not provided any evidence as to the mutation done on ligase or the extrapolation, if any, to a genus as broadly claim.

If an appellants choose to rely upon general knowledge in the art to render his disclosure enabling, the appellants must show that anyone skilled in the art would have actually possessed the knowledge, In re Lange (CCPA 1981) 644 F2d 856, 209 USPQ 288. There is no explicit description in the specification as to the method of labeling any biotin analog with a mutated biotin ligase along the 321-residue protein sequence. Applicant can rely upon prior art which would enable one skilled in the art to glean therefrom the necessary information to render the specification. enabling with respect to the first paragraph of 35 USC 112 but the burden is on applicant to point out precisely where enablement lies in such disclosure. In re Albrecht II (CCPA 1975) 185 USPQ 590. However, not everything which may be cited as prior art to preclude the grant of a patent can be equated with common knowledge for the purposes of meeting the enablement requirement of 112.

Amount of Direction Provided by the inventor: The specification provides definitions, sequence and/or structural information, and examples of biotin ligase mutants, biotin analogs acceptor peptides, and target proteins. The sequence of

wild type biotin ligase was known, and the specification provides sufficient guidance regarding the location and nature of mutations as well as numerous examples of biotin ligase mutants. The synthesis of such mutants would have been routine based on the sequences provided in the specification. The specification also provides the structure of a number of biotin analogs as well as guidance as to how to make such analogs. (See Figs. IB, 4 and 5.) The acceptor peptide sequences and functions were also known as was the ability to conjugate them to any target protein. The Examiner doubts the range of proteins that can be labeled with the biotin analogs and biotin ligase mutants of the invention. As disclosed in the specification and in the Schatz patents of record, virtually any protein can be labeled provided it comprises the acceptor peptide. As taught in the specification, the biotin interaction and activation domain is located at amino acid residues 83-235 and is physically separated from the acceptor peptide binding site located within amino acid residues 1-26.

In reply, the specification recites only some of the positions along the 321-ligase protein sequence. The kind of amino acids for each of these positions has not been taught in the specification. In all likelihood, it would be possible to mutate each of the positions of the 321-residue. What is needed

to guide a skilled artisan is the kind of amino acid substitutes necessary for mutation since applicant states that this has not been known in the art at the time of filing.

Level of Predictability in the Art: The level of predictability in the art is also exemplified by the Schatz patents of record. The use of wild type biotin ligase and biotin to biotinylate a target protein that is conjugated to an acceptor peptide was established in the art at the time of filing.

In response, the level of skill according to Schatz is the use of the wild-type ligase not a mutation of the ligase. However, see Kwon (J. Mol. Biol.) as to the level of skill with respect to the mutation of ligase.

Working Examples: The Examiner states that the specification fails to provide working examples. Applicant disagrees and points the Examiner to Table 1 which demonstrates the incorporation of biotin analogs using biotin ligase mutants to the complete or partial exclusion of biotin incorporation. Notwithstanding these data, however, the claimed invention is enabled by the specification since the courts have previously held that a specification need not contain a working example if the disclosure of the invention is adequate to allow one of ordinary skill to practice it without undue experimentation

(i.e., if the disclosure is otherwise enabling). In re Borkowski, 422 F.2d 904, 164 USPQ 642 (CCPA 1970).

In reply, the working example relates to specific substitutions of the 321 long protein. It is not apparent from the data as to its correlation to the broad claimed genus mutated at every position with any amino acids.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4, 30-33, 35, 37-38 and 53-56, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Schatz in view of Oh (5,168,057) or Huber et al (5,952,185) and repeated below.

Schatz discloses at col. 3, line 35 up to col. 4, line 30 a method for producing biotinylated proteins in vitro and in recombinant host cells. Schatz discloses that biotinylation peptide added to any protein expressed in E. coli with a sufficient time of retention in the cytoplasm to permit BirA to act. If high expression levels of biotinylated protein are desired, then one can readily overexpress the BirA protein at the same time Host cells that lack an endogenous biotin protein ligase (called a biotinylation enzyme) can be transformed with a vector that codes for expression of the birA gene to provide or enhance their ability to biotinylate recombinant proteins.

Where, due to the conservation of the recognition domains, the endogenous biotin-protein ligase of other non-E. coli cell types recognize the novel biotinylation sequences, no such recombinant expression of a biotinylation enzyme is required. One can also perform the biotinylation reaction in vitro using a biotinylation enzyme such as purified BirA, biotin, and biotinylation sequence peptide-tagged proteins, which proteins may be either produced in recombinant host cells or by in vitro translation. One can also use biotin analogues, such as 2-iminobiotin, which has a lower affinity for avidin than biotin and so may be preferred for some applications, in place of biotin, in the method. Schatz does not disclose a biotin analogue as e.g., azide biotin. However, Oh discloses at col. 31, lines 10-23 that commercially available biotin-NHS (5 atoms added to spacer) or biotin-X-NHS (12 atoms added to spacer) may be used. Alternatively, Bis-caproamidobiotin (biotin-X-X-NHS) may be conveniently used where 19 atoms are desired to be added to the spacer. All of these preactivated biotin derivatives readily condense with the omega-amino group of the lysine starting spacer moiety to yield the desired boronic acid-azide biotin (guiding member-reactive member-intended label) tridentate conjugate. The tridentate conjugate shown in FIG. 9 results where biotin-X-X-NHS is employed in the final

derivatization step. Huber discloses at col.3, lines 38-41 that photo-activatable biotin derivatives are known. EP-A-0 155 854 and EP-A-0 187 323 describe azide-substituted phenyls/nitrophenyls which are coupled to biotin_via an amine-containing linker. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use in the method of Schatz an azide-biotin analog as taught by either Oh et al or Huber et al. Azide-biotin tags have been known to have conventionally used in the art. One would have been motivated to use an analog since analogs are known in the art to have improved property as compared to the wild or native type compound.

Response to Arguments

Applicant requests clarification as to the Schatz reference employed in the above 103 rejection. Nevertheless, applicant recognizes that the Schatz Patents (5,932,433, 5,723,584 and 6,265,552) has identical specification. Applicant states that even if appropriate, the combination of references does not result in all the limitations of the pending claims, all of which at a minimum require a mutant biotin ligase.

In response, the omission of the specific Schatz Patent used in the 103 rejection is regretted. It is the 6,265,552 reference that was used in the rejection. (This is nonetheless

immaterial as applicant states the specification of the three patents is identical).

Attention is drawn to the Schatz Patent ('552) at Example 6 which discloses a mutant of the instant BIR enzyme i.e., the fragment of the enzyme. The claimed wild-type amino acid is an inherent property of the same enzyme, BIR, used by Schatz. As applicant stated above "...Biotin ligase is BirA, the 321 amino acid sequence of which is provided as SEQ ID NO:1. The specification teaches that the biotin ligase mutant can have various mutations, including addition, deletion or substitution of one or more amino acids." (Emphasis added). Accordingly, even Schatz, alone or in combination with the other prior art render the claimed invention prima facie obvious.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[Protein Science, 2000 (I) or (II)]. [Applicant is not entitled to the instant filing date since applicant has not specifically disclose the amino acid substitute at position 118 of the biotin ligase].

Each of the Kwon references discloses a method of labeling target protein using BIR ligase with mutations at positions 118, 115 and 119. See e.g., Table 2, at page 560 and the detailed method at Materials and Methods section, pages 568-569. Kwon (II) basically discloses the same method employing the same mutations. See e.g., page 1530. Accordingly, the specific process steps of Kwon having specific mutations along the BIR sequence fully meet the broad claimed method.

Claims 1, 30-33, 39-40 and 53-56, as amended, are rejected under 35 U.S.C. 102(a) as being anticipated by Rhee et al (Protein Science). [Applicant is not entitled to the instant filing date since applicant has not specifically disclose the amino acid substitute at position 118 of the biotin ligase].

Rhee discloses a method of biotinylating a target protein using the mutant of Bir A. See e.g., page 3044, Results section up to page 3049. See specifically the specifics of the method at page 3048 up to page 3049. The claimed amino acid of the wild-

type BIR, which as applicant admits is known in the art, is disclosed page 3044 referring to the Wilson or Weaver reference.

Claim 52 is free of prior art and would be allowable if incorporated into the base claim 1.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 3, 5-29, 34, 36, 41-51, 57, 81, 95, 111, 122 and 146 drawn to a non-elected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
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